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Pulmonary Calcification and Negative Tuberculin Reaction.—The literature relating to the presence of calcified pulmonary lesions without tuberculin sensitivity is reviewed. This type of calcification is particularly prevalent in the eastern slope of the Mississippi river basin ranging from 27 to 83 per cent in different states of this region. Only 10 to 50 per cent of these calcified lesions are accompanied by tuberculin sensitivity. The absence of tuberculin allergy in these instances has been interpreted as evidence for the nonspecificity of the tuberculin reaction. However, Gass observed the development of calcified lesions in children in Tennessee without concomitant tuberculin sensitivity. Since children in this section failed to react to coccidioidin, infection with *Coccidiodes immitis* as the agent responsible for the calcification was excluded. Independently of Palmer's observation of the rôle of *Histoplasma capsulatum* in pulmonary calcification, it was found in a study of 181 Tennessee children that the incidence of positive reactions to histoplasmin is more frequently correlated with pulmonary calcification than with positive tuberculin reactions. Thus at the age of 5 to 9, 63 per cent had positive histoplasmin reactions, 38 per cent showed pulmonary calcifications and only 14 per cent had positive tuberculin reactions. In a known case of infection with *Histoplasma capsulatum* a positive reaction to histoplasmin developed. These observations do not exclude other agents as responsible either for the pulmonary calcifications or for the positive histoplasmin reactions because of the possibility of cross reactions between various fungi. They nevertheless suggest a possible etiologic relationship between benign histoplasmoses and pulmonary calcification and point directly to the likelihood that much pulmonary calcification observed in this region is of nontuberculous origin.—*Pulmonary Calcification in Negative Reactors to Tuberculin, A. Christie & J. C. Peterson, Am. J. Pub. Health, November, 1945, 35: 1131.*—(*M. B. Lurie*)

X-ray Findings in Negative Tuberculin Reactors.—Photoroentgenograms of 2,000 individuals with negative Mantoux tests revealed presumably tuberculous lesions in 40 cases (2 per cent). On closer analysis certain findings, such as hilar adenopathies and widening of the mediastinum, had to be considered as nontuberculous. The remaining cases (0.25 per cent) were represented by tracheobronchial adenopathies, gangliopulmonary processes and infiltrations. Further studies in some of the latter cases showed, later on, a positive Mantoux test, thus proving the existence of a preallergic phase. The overall results of these investigations showed that the preallergic phase has to be taken into consideration in age groups below 20 years; after this age it can be disregarded. In 196 cases pleural and pulmonary changes were found, such as pleural thickening, indurations, calcifications, which could be considered as tuberculous sequelae. The negative tuberculin reaction in these cases can be interpreted as latent allergy (Saye), an expression of biological healing. The negative tuberculin test acquired great diagnostic importance in one case of pulmonary mycosis, in one case of bronchiectasis and in one case of hydatid cyst.—

Imagen radiografica pulmonar de torax de dos mil reactores negativos a la tuberculina, A. R. Gines & S. D. Martinez, Hoja tisiol., September, 1944, 4: 241.—(*L. Molnar*)

Negative Tuberculin Reactions.—Negative tuberculin reactions are obtained under various conditions. First, in persons who have not had a tuberculous infection (normergy). The number of such persons in countries of massive tuberculinization is small; the incidence of negative tuberculin reactions diminishes with age. In persons who had been exposed to infection, or in presence of pulmonary findings resembling those usually observed in primary infection, a preallergic condition may be suspected. The incidence of this condition is certainly small: in 2000 cases of negative tuberculin reactions the author has definitely proved the existence of a preallergic status in only 0.45 per cent. Finally, it has been demonstrated that with the biological healing of the tuberculous process positive tuberculin reactions may turn negative. Out of 269 cases of negative tuberculin reactions there were 24 with the presence of calcifications. This condition is called "latent allergy" (Sayé) or "extinction of allergy." In these cases the tuberculin reactions are negative, but the individual has maintained a certain capacity to reaction, which is manifested by a shortening of the preallergic condition after a new exposure. Latent allergy is called by some authors "secondary positive anergy," in contrast to the secondary negative anergy which is said to be characteristic of the terminal stages of tuberculosis. The author's experience does not bear out the assumption that such a condition exists and he feels that the question should be reinvestigated.—*Interpretacion de las reacciones tuberculinicas negativas, A. R. Gines, Hoja tisiol., December, 1944, 4: 325.*—(*L. Molnar*)

Loss of Tuberculin Sensitivity.—The case of a 13 year old boy is presented in whom a primary pulmonary tuberculosis had been diagnosed. The skin test was positive at that time, but repeated subsequent tests proved that the skin sensitivity decreased progressively until five years later the skin test was and remained negative.—*Extinction des réactions tuberculiniques après une primo-infection, M. Chevalley, Bull. et mém. Soc. méd. d. hôp. de Paris, 1940, No. 38.*—(*G. Simmons*)

Histoplasmin Reactors.—Histoplasmin is a sterile broth filtrate of a culture of *Histoplasma capsulatum;* blastomycin is prepared from broth cultures of *Blastomyces dermatitidis*, coccidioidin from cultures of *Coccidioides immitis*, and haplosporangin from cultures of *Haplosporangium parvum*, a fungus causing pulmonary disease in wild rodents. Histoplasmin injections had no toxic effect on guinea pigs and mice. Normal guinea pigs did not react to intracutaneous reactions of histoplasmin and blastomycin. Of 39 guinea pigs with experimental histoplasmosis, 32 reacted to histoplasmin in a dilution 1:100; of the remaining 7, 5 reacted to a 1:10 dilution. Nine rabbits with experimental histoplasmosis reacted to histoplasmin. Of 8 guinea pigs experimentally infected with *Blastomyces dermatitidis*, 8 reacted to histoplasmin, 7 to blastomycin and one to coccidioidin. Of 7 experimentally infected with *Coccidioides immitis*, 2 reacted to histoplasmin, and 6 to coccidioidin. Of 7 guinea pigs experimentally infected with *Haplosporangium parvum*, 6 reacted to histoplasmin, 6 to blastomycin, 4 to coccidioidin, and 5 to haplosporangin. Of 9 rabbits with experimental histoplasmosis, 9 reacted to histoplasmin and 8 to blastomycin. One hundred and thirty-six hospitalized persons, of whom 69 had atypical pulmonary lesions, were tested. Fifty-five (40.4 per cent) reacted to histoplasmin, 35 (25.7 per cent) reacted to blastomycin and 34 (25 per cent) reacted to both antigens. A positive histoplasmin reaction may be due to sensitization to either *Histoplasma capsulatum, Blastomyces dermatitidis* or some other unknown antigenic agent. —*Studies of the Rôle of Fungi in Pulmonary Disease. I. Cross Reactions of Histoplasmin, C. W. Emmons & B. J. Olson, Pub. Health Rep., November 23, 1945, 60: 1383.*—(*G. C. Leiner*)

Albert Calmette.—A short biography and a moving tribute to Albert Calmette whose last injunction to the author was, "My son, I am dying. Take care of my wife. Do not leave for America. Fight for BCG."—*La immunidad antituberculosa y la vacunación con el B.C.G., A. Sáenz, Rev. tuberc. Habana, January-March, 1945, 9: 5.*—(*R. Kegel*)

BCG Vaccination.—During the last five years, increasing interest has been aroused in vaccination. Recent work has proved the harmlessness of BCG for man, but the ideal method of administration has been in doubt. Specific protection against virulent infection is produced only when BCG vaccine is used parenterally. There is no biological test available in man to disclose the degree of acquired protection. Earlier investigators have arrived at the conclusion that oral administration was of little value, there being only 7.6 per cent conversion of tuberculin reaction. Subcutaneous injection was then begun in 0.25 mg. doses with resultant extensive local necrosis; reduction of dosage to 0.01 mg. resulted in 90 per cent tuberculin conversion in a three months' period. This method was still accompanied by a 30 per cent incidence of suppurating abscesses of regional lymph nodes. Intracutaneous injection of 0.01 to 0.05 mg. resulted in 93 per cent positive reaction in six to seven weeks. It was necessary, however, to revaccinate 23 per cent of these subjects before conversion occurred; the incidence of suppurating abscesses between 1939 and 1942 was between 23.6 per cent and 10.4 per cent, respectively, by the use of this method. Birkhaug repeated the work of Rosenthal, using 5 mg. per cc. of BCG with a series of guinea pigs, and found that the regional lymph nodes became palpably enlarged for five to six months after vaccination; the tuberculin test became positive in all animals in four weeks and remained so for fourteen months. The degree of tuberculo-resistance was measured by infecting 12 animals with 0.001 mg. of a highly virulent human tubercle bacillus and 12 control animals. All animals were killed in eight weeks and their tuberculous lesions compared quantitively according to the weight and volume of various organs. Control animals presented advanced caseo-necrotic lesions at the inoculation site and adjacent lymph nodes, numerous tubercles in the spleen and scattered tubercles in the liver and lungs. The vaccinated animals presented a small infiltrated area at the inoculation site without abscess; there were slightly enlarged adjacent lymph nodes and no macroscopic lesions in the internal organs or lymph nodes. Birkhaug, in 1940, was next encouraged to transfer the multiple puncture BCG vaccination to man. A group of 246 adults and 38 children were vaccinated by the use of an 8-needled apparatus. The vaccine suspension contained 5 mg. BCG per cc. The initial traumatic swelling subsided in three to five days and red papules developed during the second week. In four to seven weeks, the papules began to desquamate and disappear without evidence of ulceration. Occasionally the axillary lymph nodes on the vaccinated side were tender and palpably enlarged. When individuals in an allergic state were vaccinated, the papules became intensely red and markedly elevated, later became confluent and pustulated and signs of intoxication became evident; 2 cases of erythema nodosum are thought to have been provoked by vaccination in allergic individuals. Of the vaccinated group, 93.7 per cent became tuberculin-positive in two weeks and 100 per cent became positive in four weeks and remained so for one year or more. In 1943, approximately 1,500 persons were vaccinated by the percutaneous method, using the automatic apparatus. Ninety-eight per cent positive tuberculin reactions with 1 mg. OT occurred two months after vaccination.—*Protective Value of the Intracutaneous and Percutaneous Methods of BCG Vaccination, K. Birkhaug, Acta med. Scandinav., 1944, 117: 274.*—(*E. R. Loftus*)

BCG Vaccination.—The author, a former associate of Calmette, writes of the development of the bacillus Calmette-Guérin from a bovine tubercle bacillus cultivated upon a bile-enriched medium for 230 generations during three years. This bacillus had lost all power

to cause disease in animals and man but was antigenetically similar to virulent tubercle bacilli. After innumerable animal experiments Calmette in 1921 began to give BCG orally to vaccinate the infants of tuberculous parents. The Pasteur Institute undertook the wide-spread distribution of BCG in 1926. In the next decade over one million French children were vaccinated. The total number of persons vaccinated in Europe, Asia and America is now over ten million. While the oral route of vaccination is official in France, the subcutaneous, intracutaneous, multiple puncture and scarification methods are used in some countries. The efficacy of BCG is proved by numerous reports from all over the world which agree in showing a reduction of the mortality from tuberculosis among vaccinated infants to one-fourth or one-fifth that of nonvaccinated infants. The tuberculous mortality rates of vaccinated nurses, soldiers and medical students are most favorably influenced by BCG.—*La vacunación preventia de la tuberculosis por el B.C.G., sus bases experimentales y su desarrollo actual, A. Sáenz, Rev. tuberc. Habana, January–March, 1945, 9: 23.* —(*R. Kegel*)

BCG Vaccination.—A review of the work of the past two decades on antituberculous vaccination with Calmette's BCG in infants, adolescents and adults confirms its innocuousness and efficacy. The immunity it confers to both animals and humans is not absolute. The more rigorously the possibility of virulent infection is excluded before and immediately after vaccination with BCG, the better are the results. It is the task of the future to examine with exactitude the conditions under which vaccinated persons develop tuberculosis and to determine the limits of BCG's effectiveness. In North America, England and New Zealand, tuberculosis mortality rates are very low as contrasted with rates of 200 to 250 per 100,000 in Central and South America. The adoption of North American control measures by Latin America is urged but these measures, because of their slow results, should be supplemented by vaccination with BCG. If recent studies on the efficacy of revaccination every two to three years are confirmed we may expect a decisive reduction in the tuberculosis mortality rates in the next twenty to thirty years.—*La vacunacion antituberculosa de Calmette-Guérin B.C.G. 1924–1944, L. Sáyé, Rev. tuberc. Habana, January–March, 1945, 9: 52.* —(*R. Kegel*)

BCG Vaccination.—The possibility of antituberculous vaccination through the respiratory route was studied. Twelve guinea pigs were held in small glass cages and exposed to a BCG aerosol (containing 0.06 to 0.07 g. bacilli) for thirty to sixty minutes on one to three occasions. Fifty per cent of the animals showed a positive tuberculin test after forty-three days, 75 per cent after fifty days, and 100 per cent after eighty days. The tuberculin allergy, however, proved to be of less than one year's duration. In a simultaneous study vaccination with BCG aerosol was attempted on 12 children under two years of age. The time of exposure was one hour in fractionated nebulizations of ten minutes. Each child received three sessions with one day's interval. The dose amounted to 0.09 g. or 0.18 g. at each session. No subsequent complications were noted. All children had been kept under strict isolation at least five weeks before vaccination and were not released before the appearance of a positive tuberculin reaction. In 4 cases the period of observation was insufficient. One case showed persistently negative tuberculin reactions, even after three subsequent intracutaneous administrations of 0.1 mg. of BCG. One case was discovered to have received a previous dose of BCG and became tuberculin-positive two weeks after vaporization, a result which permitted no conclusions. The 6 remaining cases showed appearance of a positive tuberculin reaction forty to sixty days after inhalation of the stronger suspension, and approximately five months after inhalation of the weaker suspension. In all cases the chest X-ray remained negative following vaccination.—*La vaccination antituberculeuse par les voies respiratoires. Aérosols et broullards de BCG, J. Troisier, J. Le Melletier & J. Sifferlen,*

Ann. Inst. Pasteur, January–February, 1944, 70: 33.—(*V. Leites*)

Bucconasal Administration of BCG.—The authors have modified the technique of Etchemendigaray for bucconasal administration of BCG vaccine. They use 0.03 g. of BCG suspended in 3 cc. of liquid. This dose is divided in three portions and given by spray within a week. Fifty-six children of more than 6 years of age were tested. Forty-three children could be followed up. Of those, 37, or 86 per cent, developed positive tuberculin tests in some cases after nineteen days, but generally around the thirtieth day. This method compares favorably with the administration of BCG by mouth or subcutaneously and is hardly inferior to the intracutaneous or multiple puncture method. It has a high power of allergization and it is not harmful. But it is still not a practical method as it takes too long a time to apply the vaccine by spray and requires the help of at least one assistant. It is impractical for children under 6 years. The danger of inhalation of BCG vaccine by the administrating physician is pointed out. Experiments with this new method in 10 animals did not result in any allergy within three months.—*El metodo bucco-nasal de administracion de la vacuna B.C.G., R. F. Vaccarezza, A. R. Arēna & A. Brisco C., An. Cáted. de pat. y clin. tuberc., June 1, 1944, 5: 134.*—(*W. Swienty*)

Pathological Changes Produced by BCG.—BCG was applied by the scarification method and the cellular processes at the site of application were studied. Slides made a few minutes after scarification showed the wound covered with numerous bacilli and invaded by a lymphatic fibrinous exudate. There was no cellular reaction as yet. Five hours after scarification the appearance of polynuclear leucocytes was noted. The wound was filled with a fibrinous coagulum containing part of the bacilli, the other part of which had been carried by the leucocytes towards areas of healthy tissue. From the third day on there was disappearance of leucocytes, which were replaced by numerous monocytes containing bacillary bodies in a stage of multiplication. In the course of the second week the lesion showed enlargement through increase in monocytes and the appearance of numerous epithelioid cells. Giant cells and lymphocytes were noted at this stage. The bacillary bodies were intracellular and showed marked multiplication. From the third week on the number of bacilli decreased through some unknown mechanism, although the lesion kept on enlarging up to the sixth week, consisting mainly of epithelioid and some giant cells. From that time there was retrogression. Eventually at the site of the scarification there was an absolutely intact epidermis with a few underlying fibroblasts.—*Les modifications anatomo-pathologiques provoquées par le BCG au niveau des scarifications cutanées, J. Bretey, Ann. Inst. Pasteur, September–October, 1942, 68: 452.*—(*V. Leites*)

Treatment of Tuberculosis with BCG.—In order to study the effect of BCG administered by cutaneous scarification on guinea pig tuberculosis, the following experiments were done: (*1*) Twelve guinea pigs were infected with virulent tubercle bacilli. Eight of these were vaccinated with BCG twice weekly. All animals were sacrificed after eight weeks. In the treated animals there was a slight retardation of the generalization of the lesions. (*2*) Twenty-nine guinea pigs were infected with virulent tubercle bacilli. Twelve of these were vaccinated with BCG on the first, fifteenth and thirtieth day. All animals were sacrificed after six weeks. There was no difference in the extent of the disease between the treated animals and the control group. (*3*) Twelve guinea pigs were infected with virulent tubercle bacilli. Seven of these were vaccinated by BCG two days later. The animals were sacrificed after eight weeks. There was no difference between the treated animals and the controls. (*4*) Twelve guinea pigs were vaccinated with BCG and five weeks later infected with virulent tubercle bacilli. Seven of these were vaccinated with BCG after two days, six weeks, eight weeks and twelve weeks. The animals were sacrificed four months after they

had been infected. The treated animals had slightly fewer lesions in the liver and in the lungs than the controls. (*5*) Twenty guinea pigs were vaccinated with BCG and ten weeks later infected with virulent tubercle bacilli. Five of these received 6 vaccinations with BCG in the following six months. Five animals were vaccinated with heat-killed human tubercle bacilli. Five animals were treated with subcutaneous injections of BCG. Five animals remained as controls. All guinea pigs were sacrificed five months after they had been infected. No difference in the extent of the disease was seen between the four groups. (*6*) The same experiment was done on 20 guinea pigs with the only difference that they received subcutaneous injections of BCG. One group remained as control and three groups were treated exactly as those in the preceding experiment. No difference was seen between the different groups.—*Influence exercée sur la tuberculose du cobaye par le BCG administré par sacrifications cutanées, L. Nègre & J. Bretey, Ann. Inst. Pasteur, May–June, 1945, 71: 161.*—(*G. C. Leiner*)

Sterilization of Tuberculous Lesions.—Sterilization of tuberculous lesions and extinction of tuberculin sensitivity are never observed in the usual guinea pig experiments, even with minimal doses of virulent bacilli. Since tuberculosis of the guinea pig is invariably fatal, no conclusions should be drawn concerning any form of human tuberculosis and especially not the latent form of bacillary infection in man. It is only in this latter form that Saenz, Ameuille and Canetti have described a frequent sterilization of lesions. However, experimental tuberculosis of the guinea pig can be made comparable to latent tuberculosis in man by inoculating guinea pigs with extremely attenuated bacillary strains. Administration of BCG to guinea pigs was found to reproduce anatomically and clinically latent tuberculosis (by latent pulmonary tuberculosis is understood the presence of a primary complex in otherwise healthy individuals). In the guinea pig experiments carried out in collaboration with Canetti complete sterilization of lesions was found after a maximum of three months with a dose of 1 mg. of BCG, and after five months with a dose of 10 mg. After a dose of 1 mg. of BCG it is rare that tuberculin sensitivity persists after a period of ten months. After 10 mg. the extinction takes place between the fifteenth and twenty-fifth month. There appear to be great individual variations in the time of disappearance of tuberculin sensitivity in animal experiments, suggesting similar conditions in human tuberculosis. A rather long interval was found between the moment of sterilization of lesions and disappearance of tuberculin sensitivity. The lesions are found sterile from the third to fourth month on, whereas tuberculin reactivity hardly disappears before the tenth or twelfth month, often even much later. This fact leads to the conclusion that during a long period of its existence the tuberculin reaction has another substratum than the presence of living tubercle bacilli in the organism. This substratum might be some colloidal modification of the cellular protoplasma produced by the sensitizing antigens, persisting long after the source of these antigens is exhausted. It is probable that similar conditions exist in man. Latent tuberculous foci are usually sterile when the stage of calcification is reached, whereas the tuberculin reaction persists much longer. In view of this fact it becomes impossible to affirm that every tuberculin reactor may develop active pulmonary tuberculosis without new infection. In another series of experiments guinea pigs were treated as above and reinfected with a virulent strain after their tuberculin sensitivity had subsided. The reappearance of tuberculin sensitivity was now markedly accelerated as compared to controls, and it was highly positive. These findings demonstrate that, after complete extinction of tuberculin sensitivity of the skin, there still persists a state of allergy in the organism in the sense of a modified reactivity. Thus, skin sensitivity to tuberculin is not the only expression of tuberculous allergy. The phenomenon of acceleration of resentization seems also to exist in man as some observations indicate.

It is finally emphasized that the above findings do not speak against the protective value of BCG, the protection created by the allergic state and the allergic state itself not being identical.—*Quelques considérations expérimentales sur les notions de stérilisation des lésions tuberculeuses, A. Saenz, Rev. de la tuberc., 1939–40, 5: 1383.—(V. Leites)*

Intracerebral Inoculation of Tubercle Bacilli.—Ten young monkeys from Guinea were inoculated intracerebrally with 0.05 mg. of tubercle bacilli of various strains. No difference was found in the pathogenic effect of human and bovine type bacilli. Death occurred with both strains three to four weeks after inoculation following a short period of prostration and somnolence. The local reaction appeared early and was of marked severity. There was involvement of the major part of the meninges and the parenchyma of the inoculated hemisphere. The cerebral parenchyma was the site of extensive cellular infiltrates consisting mainly of polynuclear leucocytes, forming real nodular abscesses which showed varying degrees of confluence. No typical tubercles were found in the parenchyma. Giant cells were rare or absent. There was no evidence of caseous necrosis. The vascular reaction was very marked consisting in new-formation of numerous capillaries and medium sized vessels in a state of dilatation and endothelial proliferation. There was marked proliferation of the glia elements. The accompanying meningitis, which was always present, showed histologically a more typical picture of tuberculosis. There was histiocytic and lymphocytic infiltration with tubercle formation. Acid-fast bacilli were scant in the infiltrates consisting of leucocytes and more numerous in the histiocytic and epithelioid areas. Avian type bacilli produced a different reaction, the encephalitic infiltrates consisting of histiocytes, lymphocytes and epithelioid cells. This strain did not produce any dissemination of tuberculosis to other organs. Animals inoculated with human and bovine type bacilli showed tubercle formation in the tracheobronchial lymph nodes, lungs, liver and spleen. Particular emphasis is laid on one case inoculated with a human type of very low virulence, isolated from a case of lupus. A large multilocular abscess was found, consisting of leucocytes in the state of fatty degeneration, surrounded by a zone of sclerosis and a zone of cleavage. There was no histological evidence of tuberculosis and no acid-fast bacilli were found. The animal showed clinically no downhill course and was killed after six months for autopsy. An analogy is seen in this case to a certain number of cerebral abscesses in man which come to operation and in which histological and bacteriological examination fails to demonstrate tuberculosis. The hypothesis is ventured that these abscesses may be due to tubercle bacilli of very low virulence, which have been gradually destroyed by local tissue reactions. —*Sur l'inoculation intracérébrale de bacilles tuberculeux et paratuberculeux chez les singes inférieurs, I. Bertrand & J. Bablet, Ann. Inst. Pasteur, March, 1942, 68: 175.—(V. Leites)*

Tuberculous Infection with One Bacillus.—The problem was studied whether one single bacillus is capable of producing tuberculosis in guinea pigs. The experiments were carried out with the micromanipulator of Peterfi. The site of inoculation was an incision in the lumbar region. The bacilli which had been isolated under the micromanipulator were suspended in saline and injected with the micropipette. All animals had a negative tuberculin reaction at the onset of the experiment. Nine guinea pigs were inoculated with one bacillus and one animal received three bacilli. Tuberculin reactions were performed repeatedly at regular intervals during the following three months. Five out of the 9 animals having received one bacillus developed tuberculosis, the starting point of which was the site of inoculation as confirmed by autopsy. The tuberculin reaction became positive during the second month after infection. The 5 other guinea pigs did not develop manifest tuberculosis but showed atypical allergic reactions as evidenced by a transitory and

attenuated tuberculin reaction. In one guinea pig the tuberculin reaction was doubtful. These animals were later utilized for other experiments with virulent infection and reacted in the same way as vaccinated animals. —*Expériences d'infection par un seul bacille tuberculeux isolé au micromanipulateur, J. Breley, Ann. Inst. Pasteur, November-December, 1944, 70: 357.*—(*V. Leites*)

Variations of the Koch Phenomenon.—Tuberculosis was induced in guinea pigs with 0.01 mg. of human type bacilli. After establishment of tuberculin allergy the response to regularly repeated reinfections was studied. The interval between the reinoculations varied between one and eight weeks. The dose was 0.1 to 1.0 mg. The following reactions were found: (*1*) In a small number of cases each reinoculation was followed by a typical Koch phenomenon. (*2*) More frequently an attenuation of the Koch phenomenon was observed, which was in some cases followed by its complete disappearance. (*3*) In a third group of cases irregularity of the reactions was noted, the animals reacting to the reinoculations alternatingly with a typical Koch phenomenon and with a simple infiltration. The reason for these fluctuations could not be found. (*4*) Another group of animals reacted on some occasions with a Koch phenomenon, on others with the formation of an abscess containing tubercle bacilli. The conclusion is drawn that the response to repeated reinoculations is variable and that the Koch phenomenon represents by no means a constant mode of reaction.—*Les modalités du phénomène de Koch au cours de la période allergique de la tuberculose du cobaye, P. Gastinel & H. Brocard, Ann. Inst. Pasteur, July–August, 1945, 71: 240.*—(*V. Leites*)

Lesions Due to Dead Tubercle Bacilli.—Intratesticular inoculation of guinea pigs with dead tubercle bacilli incorporated in vaseline oil produced pulmonary lesions of greater extent than subcutaneous inoculation. The lesions produced by human and bovine strains were identical. After intratesticular inoculation of rabbits with dead bovine bacilli death occurred within thirty to sixty days with massive pulmonary lesions consisting of large areas of caseation and hemorrhagic infiltration. The lungs were markedly hypertrophic. Inoculation of dead bacilli of the human type did not produce death and the pulmonary lesions were insignificant. With dead avian bacilli the pulmonary lesions were of moderate intensity, miliary and hemorrhagic in character. Death occurred frequently. The pulmonary lesions produced by all these strains resembled closely the lesions produced by the corresponding bacilli in the living state. Separate injection of dead bacilli intravenously and of vaseline oil intratracheally, intraperitoneally, or into the testicle, often produced lesions which were in all respects comparable to the ones above described. These lesions developed even if the bacillary injection was performed from five to thirty days after the instillation of oil. Intratesticular injection of dead BCG in vaseline oil produced pulmonary lesions which were only slightly less extensive than those produced by dead bovine bacilli of virulent strains. Intratesticular inoculation of living BCG in oil had the same effect as dead BCG. Living human bacilli administered in the same way did not give stronger reactions than dead human bacilli. It is concluded that the physico-chemical constitution is of the greatest importance in determining the pathogenic power of tubercle bacilli.—*Les propriétés pathogènes des bacilles tuberculeux morts, enrobés dans l'huile de vaseline et injectés par voie testiculaire. Leur apport aux notions de spécificité et du virulence du bacille tuberculeux, A. Saenz & G. Canetti, Ann. Inst. Pasteur, July, 1940, 65: 18.*—(*V. Leites*)

Artificial Pleural Adhesions.—Many surgical interventions require the presence of adhesions between the parietal and the visceral layers of the pleura. Thoracotomy for pulmonary abscess, hydatid cyst, the Monaldi operation, sometimes lobectomy and pneumonectomy, cannot be performed without there being previous adhesions established. Chronic or recurrent spontaneous pneumo-

thorax, nonexpandable artificial pneumothorax as well as pleural exudates also make it necessary to obliterate the pleura cavity. Extrapleural methods to establish adhesions are based on the principles to irritate the serosa with certain substances or foreign bodies and cause a local inflammatory reaction. The adhesions so obtained are generally partial. The intrapleural method may establish a complete symphysis between the two layers of the pleura. This method is based on the principle of causing an aseptic pleurisy. This may be obtained by insufflation or injection of powders, of biological products or irritating chemical substances. There is general consent that the more intense the reaction as shown by pain and temperature, the greater the danger of sudden exudates and pulmonary complications. If the reaction is slight, the adhesions are either too few or even completely absent. It is necessary to withdraw the air by continuous suction immediately after installation of the irritating substance so that both layers of the pleura stay in intimate contact. This is easy if the lung can readily be expanded, but is difficult to obtain in the presence of fluid or if there is a thick fibrotic pleura. The authors have used iodized oil in a case of spontaneous pneumothorax and bronchopleural fistula with complete cure. In another case of spontaneous pneumothorax in an old syphilitic, quinine chlorhydrate and urea were successful after injections of blood, talcum and gomenol had been tried unsuccessfully. In a third case, a therapeutic pneumothorax was discontinued but the lung did not reëxpand. Six injections of sodium morrhuate established enough adhesions for obliteration of the pleural space. These observations show that the same substance may be successfully employed in one case and may be unsuccessful in another. In all 3 cases, a more or less abundant exudate, which was well tolerated, preceded the pleural fusion. A reactivation of the tuberculous lesion by the irritating substance was not observed in the third case. The authors believe that persisting fluid in the pleural cavity makes an artificial pleural fusion impossible. A pleurisy with effusion of long standing changes the structure of the pleura. A marked tolerance is established against any substance introduced for irritating purposes. To obtain adhesions the concentration of these substances would have to be so strong that serious damage would be done to the tissue. In these cases a thorocoplasty is inevitable.—*Consideraciones sobre sinfisis pleural artificial, A. C. Artagaveytia & L. E. Matos, Rev. de tuberc. d. Uruguay, November 4, 1944, 12: 237.*—(*W. Swienty*)

Paratubercle Bacilli.—A comprehensive review of the literature on paratubercle bacilli is given. The original contribution consists in studies on the modifying effect of fatty substances on lesions produced by paratubercle bacilli in laboratory animals (guinea pigs, rabbits, white rats, chickens). Seven strains of paratubercle bacilli of different virulence were used. The first series of experiments were performed on guinea pigs with the bacillus P, isolated from the pus of a cold abscess. Subcutaneous inoculation of a culture of P bacilli in a dose exceeding 1 mg. produced the formation of a small abscess which regressed spontaneously without involvement of the regional lymph nodes. With doses over 20 mg. cultural studies sometimes revealed the presence of bacilli in the parenchymatous organs, but no definite lesions were found. Inoculation of the same bacilli emulsified in paraffin oil produced different lesions. The local abscess appeared earlier and was more marked. An ulceration developed ten to fifteen days later with formation of an enormous chancre, persisting for two months. The regional lymph nodes showed hypertrophy and caseation. The spleen was slightly hypertrophic. The lungs showed granulations without caseation. The pus of the local abscess revealed numerous acid-fast bacilli. With intraperitoneal inoculation aqueous solution of P bacilli produced very slight lesions without tendency to dissemination. Inoculation of 1 to 5 mg. of bacterial culture in oily emulsion produced constantly very extensive lesions with subsequent death of the guinea

pigs within thirty days. The majority of the animals died between the eighth and fifteenth day. In all cases the blood culture was positive for paratubercle bacilli five to six days after inoculation. Autopsy revealed consolidations in the lungs, caseous-pneumonic in nature. The tracheobronchial lymph nodes were hypertrophic and partly caseous. An abundant pleural effusion was always present. There was a marked peritonitis with formation of thick false membranes. There was hypertrophy and caseation of the mesenteric lymph nodes. All lesions showed the presence of acid-fast bacilli, often grouped around a drop of oil. Mixtures of paraffin oil and bacterial culture were also injected into the lymph nodes. Death occurred within eight to thirty days. The lungs showed similar lesions as with intraperitoneal injection. The lymph nodes showed massive caseous lesions. Instead of injecting mixtures of bacteria and oil another series of experiments utilized the method of separate administration of these two substances. The result was the development of extremely extensive lesions at those points in the organism where bacilli and oil came in contact. Thus, subcutaneous injection of oil and simultaneous intravenous injection of bacilli produced a large caseous abscess at the site of the oil injection with involvement of the lymph nodes. Necrotic granulation tissue was present in the lungs. Similar experiments were conducted with separate injection of oil and bacilli by various routes (intraperitoneal injection of oil with simultaneous intravenous injection of bacilli, intraperitoneal injection of oil and intravenous injection of bacilli two weeks later, intravenous injection of bacilli and subsequent intratracheal injection of oil). In all cases the activating influence of paraffin oil was evident: the paratubercle bacilli were found to establish themselves and to multiply considerably at the site of the oil deposits, producing extensive caseous lesions. No similar lesions were found in controls in which oil alone or bacilli alone had been injected. Similar results as in guinea pigs were observed in the rabbit and the white rat. The chicken showed reactions of much lesser degree. Other fatty substances than paraffin oil were also found to have a stimulating effect on the pathogenicity of paratubercle bacilli. Lesions produced by paratubercle bacilli in the presence of fatty substances were found to have a rich bacillary content in contradistinction to lesions produced by bacilli in aqueous solution. The stimulating effect on bacterial multiplication was further confirmed by the following experiments: very small doses of P bacilli emulsified in paraffin oil were inoculated. Aqueous solutions of 0.2 mg. and below did not produce any pathological effect; 0.02 mg. in oily suspension produced death between the tenth and twentieth day with caseous lesions containing numerous bacilli. Doses of 0.01 and 0.0001 mg. rarely produced death of the animals, but they all showed pulmonary lesions rich in bacilli. The following assumptions are made to explain the mechanism of the stimulating effect of fatty substances on pathogenicity: (*1*) the oil extracts from the bacterial cell contain toxic substances of unknown chemical composition, (*2*) the incorporation of bacilli in fatty substances produces a slowing of bacillary disintegration and a more prolonged absorption into the organism, (*3*) increased toxicity of the bacterial effect due to additional irritation by the fatty substances themselves.—*Contribution à l'étude des bacilles paratuberculeux. I. Propriétés pathogènes, R. Laporte, Ann. Inst. Pasteur, November, 1940, 65: 282.*—(*V. Leites*)

Lesions Due to Paratubercle Bacilli.—Histological studies of lesions produced by paratubercle bacilli revealed a marked resemblance with true tuberculous lesions. This analogy was still more outspoken if sufficiently virulent paratubercle bacilli were inoculated in oily suspension, or if the bacilli, administrated in saline, encountered in the lungs drops of oil, which had been introduced by another route. After parenteral inoculation the most important lesions were found in the lungs. Liver and spleen were relatively little involved. (Guinea pigs, rabbits and rats had been used for these investigations.)

The elementary pulmonary lesion was found to be of an exudative character with formation of pneumonic areas of various extent. The alveolar exudate consisted in the first stage of polynuclear cells, monocytes and large histiocytic elements, the latter becoming more and more prevalent. These histiocytes assumed in the course of the pathological process often an epithelioid aspect. They also were found to contribute to giant cell formation. Foci of epithelioid and giant cells showed often the typical structure of a tubercle with a surrounding area of lymphocytes and plasma cells. These lesions were found to be very poorly vascularized and showed areas of caseous necrosis. At all stages numerous acid-fast bacilli were present in the lesions. There was a marked tendency towards healing by fibrosis. Another comparison was made between paratubercle bacilli and true tubercle bacilli: the cytological reaction of the peritoneum was studied in the guinea pig after intraperitoneal inoculation of (*1*) virulent bovine bacilli, (*2*) BCG, (*3*) different strains of paratubercle bacilli. Comparison of diagrams indicating the time since inoculation and the cellular response showed that the general tendency of the reaction was the same in all investigated strains: (*1*) A first stage with predominance of polynuclear neutrophil cells. Intensity and duration of this phase were found identical, regardless whether virulent or paratubercle bacilli were used. (*2*) In the second stage the polynuclear cells were succeeded by monocytes with marked macrophagic properties. (*3*) A period of lymphocytosis followed, the duration of which depended on the virulence of the strain. Inoculation with a virulent strain produced very marked lymphocytosis which persisted until the death of the animal. With nonvirulent strains the lymphocytosis was of moderate degree and returned gradually to normal.—*Contribution a l'etude des bacilles paratuberculeux. 2. Histo-cytologie des lesions paratuberculeuses, R. Laporte, Ann. Inst. Pasteur, December, 1940. 65: 415.*—(*V. Leites*)

Virulence of Bovine Bacilli.—Experiments were made with 5 strains of bovine tubercle bacilli derived from cases of human and animal tuberculosis. In analogy to the Calmette-Guérin procedure regular transplantations were made every fifteen days on bile-potato medium and the modifications of virulence were studied. Besides the known fact of progressively diminishing virulence in the course of these transplantations, a special phenomenon was noted consisting in a dissociation of pathogenicity for the guinea pig and the rabbit. Thus, after 30 to 50 transplantations these bovine strains became totally or partially nonpathogenic for the guinea pig, whereas they remained considerably virulent for the rabbit for a certain period of time. A second phenomenon was observed consisting in what the author calls the "toxic" quality of the pathogenic effect on rabbits. Intravenous injection of bovine strains before transplantation on bile-potato medium produces in the rabbit miliary tuberculosis, especially of the lungs and kidneys. Inoculation with strains growing for more than one year on bile-potato medium produced death by tuberculosis of the "Yersin" type within twelve to twenty-eight days. On autopsy the lungs showed infiltrations in the interstitial tissue, consisting of polynuclear cells and histiocytes associated with intraälveolar edema. The kidneys showed simple "toxic" nephritis. There was no evidence of miliary lesions anywhere, which are so characteristic of bovine infections in the rabbit. On the other hand, a resemblance is seen to the infection of the rabbit with the avian type bacillus, which also produces fatal tuberculosis of a more toxic character without any formation of typical tuberculous lesions in the organs.—*Modifications de la virulence du bacille tuberculeux bovin au cours des réensemencements successifs sur pomme de terre bilié, F. van Deinse, Ann. Inst. Pasteur, March, 1941, 66: 191.*—(*V. Leites*)

Tuberculosis in Cats.—Ten strains of tubercle bacilli were isolated from cats which had died of tuberculosis. All colonies appeared to

be of the smooth type. After the first few transplantations on potato glycerine medium the colonies developed badly or not at all. Only the three oldest cultures (ten and eleven months) gave rise to colonies of the rough type. The interval between inoculation and appearance of the first colonies averaged four weeks. All these features were taken as evidence that the isolated bacilli belonged to the bovine strain. However, the proof of intravenous injection in the rabbit could not be carried out because of external circumstances. It is believed that tuberculous infection in cats is almost exclusively of the bovine type and originates from ingestion of products containing virulent bovine bacilli. The primary complex was mostly found in the gastro-intestinal tract. A review of the literature is given corroborating this view.—*Recherches sur la fréquence des différents types de bacilles tuberculeux dans l'infection spontanée du chat, J. Verge & F. Senthille, Ann. Inst. Pasteur, February, 1942, 68: 114.*—(*V. Leites*)

Attenuation of Tubercle Bacilli.—Experiments were performed with two strains of bovine and four strains of human type bacilli regarding the attenuating effect of bile-potato medium. Transplantations were made every fifteen days, according to the usual methods. The pathogenicity of bovine strains was evaluated by subcutaneous inoculation in the guinea pig and intravenous injection in the rabbit. In all cases a progressive and considerable lowering of the pathogenicity was found after prolonged growth on bile medium. The decrease of virulence developed gradually. At first there was progressive increase of the minimal lethal dose. Later, an identical massive dose produced less and less severe infection, the parenchymatous lesions becoming more circumscribed and showing increasing tendency towards healing. Finally there was a more and more strict blocking of the inoculated bacilli in the connective tissue and in the regional lymph nodes. However, the bacilli conserved a pronounced capacity of producing local lesions. It is believed that the attenuation by bile developed the more rapidly, the weaker the pathogenicity of the strain at the onset of the experiment. Transplantations were carried out between the years 1927 and 1940. A detailed protocol is given of the periodically repeated animal inoculations throughout the years, demonstrating the progressive loss of virulence. Thus, in 1927, 0.01 mg. of the bovine strain "Vallée" inoculated intravenously into the rabbit and subcutaneously into the guinea pig produced death in the animals after two and a half months. In 1940, after 192 transplantations on bile-potato medium, 1 mg. of the same strain was injected in the guinea pigs. The animals remained well and were killed for autopsy after seven to eight months. No visceral lesions were found. There was a small abscess at the site of inoculation and a slight hypertrophy of the regional lymph nodes. Analogous results were found in all other experiments with growth on bile media. The bovine strain Vallée was furthermore cultured on potato medium in a 1 per cent solution of bile salts. The results regarding attenuation were comparable to those obtained on bile-potato medium. Attempts at antituberculous vaccination were carried out with the attenuated strains. Four investigated strains (two bovine and two human types) all produced a definite resistance against a virulent reinfection, the results were however variable as to the degree of protection. The number of transplantations on bile media did not seem to be relevant for the vaccinating power of the attenuated cultures.—*Essais d'atténuation de bacilles tuberculeux par culture sur pomme de terre bilié, A. Boquet & Mme. A. de Grolier, Ann. Inst. Pasteur, January, 1942, 68:* 5.—(*V. Leites*)

S-forms of Acid-fast Bacilli.—Blood cultures performed in 2 cases of active pulmonary tuberculosis in children yielded acid-fast bacilli resembling in form, size and cultural properties the S-form of tubercle bacilli. The culture was grown on egg medium according to the method of Löwenstein. These bacilli had numerous properties in common with tubercle bacilli: their inoculation produced tuberculous allergy in laboratory animals, as evidenced by

the development of a positive tuberculin reaction. Furthermore, these bacilli produced tuberculin. Skin tests performed with concentrated broth filtrates and with tuberculin gave identical reactions. These bacilli were not of the avian type, being nonpathogenic for the hen and the rabbit. Their main characteristic was their generally low virulence. In the guinea pig subcutaneous injection of 0.1 mg. produced no general nor local reactions. Subcutaneous injection of 1 mg. produced after two weeks a circumscribed nodule of pea-size, which showed no ulceration and went on to absorption. Inoculation of 10 mg. gave a more pronounced local reaction with formation of a caseous abscess the pus of which contained numerous acid-fast bacilli. Similar reactions were found in monkeys. The morphological resemblance of these S-forms with the true tubercle bacilli combined with their low virulence led the authors to investigations regarding their possible immunizing properties. Guinea pigs were inoculated subcutaneously and intraperitoneally with 1 and 10 mg. of S-type bacilli. Three months later they were given 0.01 mg. of a virulent human strain, which killed control animals after sixty to eighty days. It was found that the immunized animals survived much longer. If they were killed four to six months after the administration of the virulent strain, some of them appeared completely free of tuberculous lesions, others were hardly affected. If animals which have been immunized as above receive an intrapulmonary injection of virulent bacilli, one observes several months later only localized caseous lesions in the corresponding lung with a tendency to fibrosis, but no dissemination is noted. Liver and spleen remain free. In conclusion the nature of the S-form bacilli is discussed. The question is left open; the authors are, however, inclined to feel that they do not represent a separate species but are rather closely related to true tubercle bacilli.—*Étude des propriétés pathogènes et vaccinantes de bacilles acido-résistants de type S (lisse) isolés du sang au cours de l'infection tuberculeuse évolutive chez de jeunes sujets, P. F. Armand-Delille & O. Gysin, Ann. Inst. Pasteur, January, 1941, 66: 5.*—(*V. Leiles*)

Congenital Lung Malformations.—A classification of congenital pulmonary malformations based on embryological criteria is presented. The broncho-alveolar tree is of endodermic origin. In the first phase of its development, approximately by the sixth intrauterine month, the bronchial tree is canalized. In the second phase the terminal bronchi lose their epithelium and become the alveolar sacs. Thus the alveoli represent the terminal part of the bronchial tree, adapted for gaseous exchange. Pulmonary malformations may be diffuse or local and are often associated with malformations in other organs. The X-ray diagnosis of pulmonary malformations is often uncertain because lesions of congenital or acquired nature may have a similar X-ray appearance. The authors differentiate between malformations that are always congenital and those lesions that may be of congenital or acquired origin. Among the former we have the agenesis of lung caused by the absence of a main bronchus. In these cases there is generally the absence of the pulmonary vessels on the affected side and they are often accompanied by cardiac malformations. An incomplete development of the bronchial tree is called hypoplasia of the bronchus. The arrest may occur at any stage of the bronchial development and correspondingly there are numerous and complex forms of malformations. Hypoplasia of a bronchus is usually associated with areas of broncho-alveolar agenesis and of bronchiectasis. The absence of one of the layers in the bronchial wall is called dysplasia. It is assumed that most of the cases of congenital bronchiectasis are due to some kind of dysplasia of the bronchial wall. The polycystic lung is a typical example of a process of congenital hyperplasia. The epithelial lining of the cysts is stratified, cylindrical, ciliated or nonciliated. Most cysts have no bronchial outlet. The clinical differentiation between polycystic lung and cystic or saccular bronchiectasis is difficult. Morelli has described a syndrome characterized by association of mal-

formations of various organs and systems. Among the processes that may be congenital or acquired, there is the group of subpleural blebs; they may be caused by scars or they may occur as congenital anomalies. The X-ray appearance of these varieties of blebs is similar regardless of the underlying pathological changes. Only histological examination may decide the etiology in such cases. Another group of processes that may give rise to diagnostic difficulties is that of bullous emphysema. The pathogenetic mechanism of this process may be inflammatory changes and scarring acting as a valve; in other cases dystrophia of the elastic tissue in some area of the lung is the cause of rupture of interalveolar septa; finally, vascular changes with consecutive tissue damage may also cause a breaking down of elastic tissue and the formation of bullous emphysema. The lung cysts of bronchogenic origin are frequently diagnosed as bullous emphysema because of similar radiological findings. The two processes show, however, sharply differentiated histological pictures: the lung cyst has an epithelial lining with the presence in its wall of cartilage and muscle, while the wall of the bullous emphysema is formed by connective tissue containing anthracotic pigment.—*Classification de las alteracions congenitas del pulmon, P. Parriel & C. Epifanio, Hoja tisiol., December, 1944, 4: 307.*—(*L. Molnar*)

Lobar Pneumonia.—Untreated lobar pneumonia in Holland is a milder disease than in the United States. Review of case histories of 356 cases treated between 1930 and 1938 shows that the mean fatality rate was 14.3 per cent. In those under 50 years of age the disease is usually mild, and no cases of death were recorded when the patient was under 50 and only one lobe was involved. The fatality rate rises sharply with age so that the mortality in patients over 50 is 43.5, whereas under 50 it is 8.2 per cent. Even though no treatment other than symptomatic was given, complications were few. Empyema was seen in 4.8 per cent of the cases, and pericarditis in 1.4 per cent. Sixty per cent of the patients had temperature drop by crisis before the eighth day.—*The Course of Untreated Lobar Pneumonia in Holland, N. Lubsen, Acta med. Scandinav., June 23, 1942, 110: 465.*—(*H. Marcus*)

Obstructive Pulmonary Emphysema Associated with Pneumonia.—Regional obstructive pulmonary emphysema in children following acute infections of the upper respiratory tract has only recently been recognized as a clinical entity. Two illustrative case histories are presented. The diagnosis depends upon the roentgenographic picture, the clinical course, and the absence of physical signs. The X-ray picture is typical, especially when the pulmonary fields are clear. There is an area of decreased density surrounded by an area of increased density. The margin is thin, dense and smooth. The area is usually ovoid and frequently varies in size from time to time. The duration may be weeks or occasionally months. The clinical course after the pneumonic lesion has cleared is entirely asymptomatic. The presence of signs or symptoms indicates secondary complication, especially otitis media. No treatment is necessary except for that of complications. No correlation has been possible with autopsy findings because of the usual benign course. Differential diagnosis must be made from lung abscess during the period of actual infection, from congenital cysts, localized pneumothorax, diaphragmatic hernia and tuberculous cavity. The mechanism involved is probably the "check valve" type of obstruction described by Jackson and Jackson. Hoover demonstrated the fact that obstruction to expiration allows the lung to become emphysematous. Van Allen demonstrated that expiratory obstruction to an entire lobe produced emphysema to that lobe, but that obstruction to smaller units did not lead to emphysema because of collateral air circulation. Therefore, obstructive emphysema is a lobar phenomenon unless something is present to interfere with collateral respiration. Collateral circulation of air is due to the combined action of pores of Kohn and to direct diffusion of air through alveolar septa. Ogawa has shown by special histological meth-

ods by which the septa are viewed in face as well as in cross section that pores actually exist. Collateral circulation is prevented by a complete septum between lobules or by inflammatory consolidation of the tissues at the border between the free and the obstructed portion of the lobe. During pneumonia conditions favorable to obstruction and to "check valve" obstruction of a bronchus are present. The bronchus is blocked by a firm mass of exudate or by viscid secretion, allowing air to flow in but not out. Eventual resolution probably occurs by slow diffusion or by removal of the initial obstruction. The length of time depends on the mechanism. Restoration to normal is eventually complete.—*Obstructive Pulmonary Emphysema Associated with Pneumonia in Childhood, J. Leopold & E. A. Kratzman, Am. J. Dis. Child., May, 1945, 69: 287.*—(*K. R. Boucot*)

Anemia and Hypoproteinemia in Pneumonia.—Two cases are reported as illustration of the importance of specific supportive therapy of pneumonia in addition to specific antibacterial treatment. Two patients with protracted, bacterial pneumonia were treated with penicillin. In both patients severe and progressive anemia and hypoproteinemia were present in spite of apparent bacteriological arrest of the infection. Large amounts of whole blood and plasma were successfully used to combat the anemia and hypoproteinemia. In addition, the importance of the measures for the maintenance of optimum gas exchange in remaining functional lung tissue is stressed. —*Anemia and Hypoproteinemia Complicating Severe Protracted Pneumonia: Treatment with Penicillin—Rôle of Specific Supportive Therapy in Recovery, S. H. Armstrong, Jr., A. C. England, Jr., C. B. Favour & I. H. Scheinberg, J. A. M. A., February 10, 1945, 127: 303.* —(*H. Abeles*)

Etiology of Atypical Pneumonia (Part II).—The isolation of a new virus from patients with atypical pneumonia, by inoculation of filtered suspensions of sputum or unfiltered suspensions of bacteriologically sterile human lung tissue into the amnion of chick embryos, has been described (Part I). Passage of the virus in chick embryos was successful, but no marked increase in virulence was observed. The development of small pulmonary lesions in hamsters or cotton rats after intranasal inoculation of material from infected chick embryos was used as a means of detecting the presence of the virus. Passage of the agent in cotton rats or hamsters was found to be impracticable because of contamination with the respiratory viruses often present in these animals. In the present paper the agent propagated in chick embryos is provisionally designated as the virus of atypical pneumonia and some of its properties are described. Five strains of the virus were isolated from human material and adapted directly to the chick embryo. Two of the strains are reported in detail. The best growth of virus, as determined by the results of intranasal inoculation in hamsters and cotton rats, resulted from material incubated for seven days or more on 11-day chick embryos. The highest dilution of chick embryo suspension producing pulmonary lesions in the test animals was not over 4×10^{-3}. Dilutions of 10^{-4} infect chick embryos. The virus was found to be unstable at room temperature and also lost activity when stored in a dry-ice refrigerator (−70°C.), unless the suspension was kept in sealed glass tubes. It could then be stored for as long as fourteen months without complete loss of activity. Filtration experiments showed the virus to be retained by collodion filters of 300 to 336 mμ average pore diameter, but passed filters of 366 to 400 mμ indicating a particle size of about 180 to 250 mμ. To show that the lesions produced in the test animals by the virus of atypical pneumonia were specific for this agent and not caused by respiratory viruses often present in hamsters and cotton rats, experiments in cross immunity were done. The atypical pneumonia virus produced pulmonary lesions in animals immunized to their own nonbacterial respiratory agents and, reciprocally, animals immunized with atypical pneumonia virus could still be infected with an animal respiratory virus. There resulted no

evidence of any cross-immunity.—*Studies on the Etiology of Primary Atypical Pneumonia. II. Properties of the Virus Isolated and Propagated in Chick Embryos, M. D. Eaton, G. Meiklejohn, W. Van Herick & M. Corey, J. Exper. Med., November 1, 1945, 82: 317.—(J. S. Woolley)*

Etiology of Primary Atypical Pneumonia (Part III).—In this section detailed data on the neutralization of the virus of atypical pneumonia by serum from persons recovered from the disease are presented. The incidence of cold agglutinins and agglutinins for an indifferent streptococcus in the serum is also discussed. For the neutralization experiments inactivated human sera were mixed with normal horse serum to give various dilutions of the former. Equal parts of the active virus were then added to each tube. After standing for twenty minutes at room temperature for neutralization to take place, samples from each mixture were inoculated intranasally into hamsters and cotton rats. The highest final dilution of serum which completely prevented the appearance of macroscopic pulmonary lesions in the animals was taken as the end point. Significant increases in neutralizing antibodies were demonstrated in 42 of a total of 69 persons with a clinical diagnosis of primary atypical pneumonia. In a specially studied group of 28 patients in which a significant antibody increase was observed, the titrations showed increases of 4- to 64-fold. Eighty-three per cent of the acute phase titers were 4 or less, whereas in 86 per cent of the convalescent cases the titers were 16 or over. In the same group of 28 patients, 17 were tested for cold agglutinins and 11 of these were found positive with (maximum) titers ranging from 20 to 1280. Agglutination with the indifferent streptococcus No. 344 was observed in 11 of the 28 cases, the titers varying from 10 to 40, a titer of less than 10 being considered negative. Previously published data have indicated that in nearly all cases of primary atypical pneumonia in which streptococcal agglutinins are present, cold agglutinins are present also. This was found to be the case in the few tests in which both forms of agglutinins were looked for. Most of the cases of atypical pneumonia included in the present study were from the Pacific Coast, but antibody increases were also found in 17 patients from the East. Geographical distribution apparently has no influence on the reactions to the disease. Patients with pneumococcal pneumonia and pneumonia caused by influenza virus type A or viruses of the psittacosis group did not have significant increases in neutralizing antibodies for the virus of atypical pneumonia. Cold agglutinins were present in 3 cases of type A influenzal pneumonia. Sera from persons with atypical pneumonia, when tested against the three most prevalent respiratory viruses isolated from cotton rats and hamsters, failed to neutralize these agents or showed no significant change in neutralization titer. It has been suggested that a toxic factor may participate in the production of pulmonary lesions in hamsters and cotton rats by the agent employed in these experiments. If this were the case the observed neutralization by human serum might be antitoxic rather than antiviral. However, the agent producing pulmonary lesions behaved more like a virus than a toxin and some evidence that the neutralization was not antitoxic was obtained in experiments in which the convalescent serum and virus were inoculated into the amnion of chick embryos with subsequent passage to hamsters or cotton rats. The data presented in this paper indicate that patients with atypical pneumonia develop in their sera an antibody which prevents the appearance of pulmonary lesions in hamsters or cotton rats inoculated with mixtures of convalescent serum and infected chick embryo tissue. There is considerable evidence that the agent producing pulmonary lesions is a virus and not a toxin.—*Studies on the Etiology of Atypical Pneumonia. III. Specific Neutralization of the Virus by Human Serum, M. D. Eaton, W. Van Herick & G. Meiklejohn, J. Exper. Med., November 1, 1945, 82: 329.—(J. S. Woolley)*

Transmission of Virus Pneumonia.—The syndrome of atypical pneumonia may be pro-

duced by bacteria, rickettsias, fungi and viruses. In the majority of cases, however, no etiologic relationship to these known agents has been demonstrated. Experiments were undertaken to study the transmission of primary atypical pneumonia to human volunteers by means of bacteria-free filtrates. Forty-two men were segregated in individual rooms. Strict isolation technique and quarantine were observed during the eight-week course of the experiment. The inoculum consisted of sputum and throat washings obtained from experimentally produced cases of atypical pneumonia. Each man received a total inoculum of 10 cc. in three equally divided doses. The material was sprayed into the nose and throat. Three of 12 men who had received inoculum filtered through sintered glass and Seitz filters developed atypical pneumonia. Three of 12 men inoculated with untreated material developed atypical pneumonia. No case of pneumonia developed in 18 men who had received autoclaved inoculum. The appearance, development and regression of the pneumonic lesions had a striking similarity to those seen in the naturally occurring disease. Cold agglutinins were found in the serum of 5 of the 6 cases of pneumonia.—*Transmission of Primary Atypical Pneumonia to Human Volunteers, Commission on Acute Respiratory Diseases, Fort Bragg, North Carolina, J. A. M. A., January 20, 1945, 127: 146.*—(*H. Abeles*)

Virus Pneumonia in Infants.—Epidemics of virus pneumonia in infants have been observed at four-year intervals in Minnesota. Premature infants were particularly susceptible. The signs consist of dyspnea, cyanosis, a white mucoid secretion on the back of the pharynx and a few râles over the involved lung portions. Numerous inclusion bodies are found in the epithelial cells obtained from the pharyngeal smear. These bodies are also found in the bronchial, bronchiolar and alveolar epithelial cells at postmortem examination. Pooled adult serum in 25 to 30 cc. doses, repeated once or twice, has been found of benefit, as well as the administration of adrenal cortical extract. Oxygen in high concentrations, preferably by tent, is the most important supportive treatment.—*Third Epidemic of Primary Virus Pneumonitis among Infants in Minnesota, J. M. Adams, Journal-Lancet, May, 1945, 65: 192.*—(*H. Marcus*)

Pulmonary Complications after Tonsillectomy.—Lung complications following tonsillectomy are probably not due to the aspiration of infected material at the time of operation. A review of 1,020 tonsillectomies at the University Clinic of Berne, Switzerland shows that the incidence of complications was highest in operations performed under local anesthesia with the patient in the semi-upright posture. Eight postoperative complications were observed in 513 cases operated under local anesthesia. The remainder of the cases were done under ether anesthesia and no complications were observed. Blood and saliva reach the trachea of tonsillectomy patients with some regularity. It could be aspirated from the trachea in 60 to 80 per cent of patients who had general anesthesia and in 38 per cent of patients who had local anesthesia. Yet the latter group had the complications, and these are seen as frequently in the upper lobes as in the lower lobes. It is likely, therefore, that the infection reaches the lung by way of the blood-stream. Of the 8 cases observed, 6 had bronchopneumonias, one a lung abscess and one developed rapidly progressive tuberculosis. All but the latter cases did well on sulfonamide therapy. The earliest constant sign of pulmonary complication is postoperative fever starting from the second to the fifth day, and the routine measure of X-raying the febrile cases will aid in early diagnosis. The incidence of postoperative complications can be expected to rise if tonsillectomy is performed shortly after a recent tonsillitis or peritonsillar abscess.—*Über Lungenkomplikationen nach Tonsillektomie, L. Rüedi, Schweiz. med. Wchnschr., May 5, 1945, 75: 389.*—(*H. Marcus*)

Acute Putrid Lung Abscess.—One hundred and seventy-two cases of acute putrid ab-

scesses of the lung have been operated in the past sixteen years at the Mount Sinai Hospital. Acute putrid abscesses are due to aspiration of infective material. The abscess develops usually within two weeks, is usually single, and the pleura over the abscess is usually obliterated. An abscess is called acute if it is less than six weeks old. After that time usually additional lesions appear, which make the results of the operation less satisfactory. Indications for operation are: severe toxemia, unusually large abscess, invasion of the pleura, stationary small abscesses, poorly draining abscesses, sustained fever, intensely fetid sputum, diabetes. For exact localization of the abscess roentgen films should be taken in various positions; the "spot" method by Rabin is always advisable. In most cases the one-stage operation was performed, consisting "of the exposure of pleural adhesions by a limited excision of a segment of one rib (in most cases), incision through adhesions at their densest portion (at which place the bulge of the abscess will often be noted), disclosure of the abscess by aspiration, its unroofing by excision of the thin compressed shell of overlying lung, and the visualization and gauze tamponade of the abscess cavity and all its recesses." The operation is followed by immediate general improvement. There were 4 deaths in 172 operations. The bronchial fistula should be maintained until the patient is completely free of symptoms and the infiltrations have disappeared on X-ray examination, which usually takes four to eight weeks. Sometimes a plastic procedure is necessary for the closure of the cavity.—*Acute Putrid Abscess of the Lung, H. Neuhof, Surg., Gynec. & Obst., April, 1945, 80: 351.*—(*G. C. Leiner*)

Shut-off Pulmonary Abscess.—The diagnosis of putrid lung abscess is frequently not made due to the absence of foul sputum. It is believed that this is caused by occlusion of the draining bronchus. This variety is called "shut-off abscess." The etiology of shut-off putrid lung abscesses is the same as that of other putrid lung abscesses. They invade the pleura more often than do abscesses with foul sputum. They can perforate into a bronchus. The main symptoms are cough and expectoration; both may vary greatly or may be missing completely. Pain due to pleural involvement is usually present. The physical examination is not of much help in making the diagnosis. The roentgenological examination reveals persistent pulmonary infiltration, but is of no aid in differentiating between a putrid and non-putrid abscess. The diagnosis is difficult and only possible if always kept in mind. Ten cases of shut-off pulmonary abscess were seen. In 5, foul sputum was expectorated between five and sixteen weeks after the onset. In 4, foul pleural fluid was aspirated. In one case the diagnosis was made at autopsy. Operation is indicated for shut-off pulmonary abscesses.—*Putrid Pulmonary Abscess without Foul Sputum: (Shut-off Pulmonary Abscess), D. Stats & H. Neuhof, Arch. Int. Med., September, 1945, 76: 154.*—(*G. C. Leiner*)

Lung Abscess—Two hundred and forty-four cases of lung abscess seen between 1932 and 1943 are reviewed. The most common localization of the abscess was in the right lower lobe, followed in order by the left lower lobe, the right upper lobe, the left upper lobe and the right middle lobe. Forty-one abscesses developed after tonsillectomy under ether anesthesia and 27 after abdominal operation under general anesthesia. In 157 cases (65 per cent) the lung abscess followed pneumonia. Other causes were: aspiration of foreign body, subphrenic abscess, congenital cystic disease, encephalitis; in 7 cases the cause was unknown. In 8 children it was caused by aspiration of a foreign body. Cultures of sputum, of material obtained by bronchoscopic aspiration and of material from the abscess revealed pneumococci in 27 per cent of the cases, *Staphylococcus aureus* in 18 per cent, fusiform bacilli in 17 per cent, hemolytic streptococci in 14 per cent, *Micrococcus catarrhalis* in 12 per cent and spirochetes in 5 per cent. The earliest and most frequent symptom was cough. Foul sputum was present in 88.6 per cent of the patients, odorless sputum in 11.4 per cent, hemoptysis in 57.8 per cent,

chills and fever in 90 per cent and chest pain in 94 per cent. There were 154 male and 90 female patients, 208 adults and 36 children. The duration of the disease was from three weeks to nineteen years. Possible preventives of lung abscess following surgery are: (*a*) good care of teeth before a contemplated operation; (*b*) avoidance of strong sedatives before and after operation; (*c*) frequent aspiration of the trachea and bronchial tree by nasal catheter; (*d*) encouraging of patient to cough after operation; (*e*) early aspiration bronchoscopy in postoperative atelectasis. In acute cases, that are of less than two months' duration, surgical drainage is advised. Of 110 acute cases, 63 had surgery and 47 no treatment other than bronchoscopy; of 134 chronic cases, 101 had surgery and 33 no treatment but bronchoscopy. A lung abscess that seems not to be draining adequately through a bronchus should have external drainage. Cautery with unroofing the cavity was done in 97 cases. In cases in which the lung is adherent the operation is done in one stage. A two-stage operation was necessary in 50 per cent of the cases. Thoracotomies for empyema were done in 37 cases. Lobectomy was done in 28 cases, pneumonectomy in 2 cases; they were done when the cavity did not heal within six months after the cautery operation. Postoperative complications were: hemorrhage, spill-over, empyema, septic spread to other parts of the body. Of the 164 patients who underwent surgical treatment, 62 per cent improved, 38 per cent died. Of 80 patients treated by bronchoscopy, 61 per cent improved and 20 per cent died.—*Lung Abscess: An Analysis of 244 Cases, A. R. Valle, Surg., Gynec. & Obst., September, 1945, 81: 278.*—(*G. C. Leiner*)

Pneumonectomy in Pulmonary Suppuration.—A 9-year-old girl was seen who had been coughing since a pertussis infection at the age of four. X-ray examination showed infiltrations in the left midlung field. The sputum was negative for tubercle bacilli. Bronchoscopy revealed no stenosis but purulent secretion from the left lower lobe bronchus. A later roentgenological examination showed atelectatic foci in the upper part of the left lung field, and pneumonectomy was therefore decided upon. Ten days before the operation pneumothorax was induced on the left. Bronchoscopic aspiration was done shortly before the operation. The operation resulted in complete cure. The findings at the pathological examination of the removed lung were: bronchiectasis and fibrosis in the lower lobe; in the upper lobe, pulmonary infarcts which probably had occurred during operation.—*Suppuration broncho-pulmonaire et pneumonectomie, J. P. Roger, J. M. Lemieux, G. L. Coté & L. Rousseau, Laval méd., June, 1945, 10: 410.*—(*G. C. Leiner*)

Coccidioidomycosis.—The incubation period of primary coccidioidomycosis varies from eight to twenty-one days. An acute, a subacute or chronic active and an arrested or healed stage can be distinguished in the course of the disease. The acute stage is characterized by respiratory symptoms, pleuritic pain, cough, hemoptysis in some cases. Chills and fever are frequent, varying from a high temperature for a few days to a low grade temperature for weeks. Sore throat is a frequent complaint. A fine macular generalized rash within the first few days is described. Physical examination may reveal signs of acute bronchitis, pneumonia or pleurisy. Within eight to fourteen days erythema nodosum and/or erythema multiforme occurs in 5 to 20 per cent of all patients. At the same time arthritic pains are observed in 30 per cent. The sedimentation rate is elevated, the leucocyte count is not significant, eosinophilia is often present. The coccidioidin skin test is positive. This initial acute infection occurs in the endemic area. The subacute or chronic active stage may be considered as that period following the disappearance of acute manifestations in which, however, there is evidence of activity as manifested by changing pulmonary lesions in chest roentgenograms. Weight loss and subfebrile temperatures are usually present. The arrested or healed stage is designated as any time following disappearance of active infection when clinically silent lesions are

demonstrated radiologically. The chest film shows a group of circumscribed lesions, nodular in character. There is a history of residence in an endemic area. The coccidioidin skin test is positive. Precipitin test and complement fixation test may be helpful. The diagnosis is eatablished by demonstration of the fungus by culture or guinea pig inoculation. The roentgenological findings during the acute stage are hilar adenopathy, patchy parenchymal infiltrations or pleural effusion. Thin-walled cavities may develop. Late cases may show linear fibrotic markings, thickened pleura, atypical parenchymal lesions or nodular lesions. The single or multiple nodular pulmonary lesions may be confused with tuberculous or metastatic lesions. The fungous lesions usually show serration of the edges. The prognosis is good. Four cases of coccidioidomycosis are reported, one was associated with tuberculosis. Attention is drawn to the problem of recognition of coccidioidomycosis in children returning from endemic areas in the Western states, where they have been sent to obtain the advantages of a dry climate in the treatment of respiratory diseases.—*Primary Coccidioidomycosis: A Possible Pediatric Problem, R. H. Kunstaster & R. C. Pendergrass, J. A. M. A., March 17, 1945, 127: 624.*—(*H. Abeles*)

Pulmonary Aspergillosis.—This is a case report of acute pulmonary aspergillosis. The patient was a 59 year old man who was admitted with the diagnosis of lobar pneumonia. Sulfatherapy was ineffective and the patient rapidly got worse and death seemed imminent. Sputum culture showed pure culture of *Aspergillus fumigatus*. Increasing doses of potassium iodide were then given, starting with 6 g. Improvement was noted practically immediately, and the dosage was increased to 45 g. daily. Recovery was rapid and uneventful and the patient remained well when seen two months later.—*Acute Pulmonary Mycosis, Elizabeth Delikat, Lancet, September 22, 1945, 249: 370.*—(*H. Marcus*)

Megamycetoma.—This is the second such case reported in the world literature. A 24 year old woman had periodical hemoptyses for seven years nearly always during the menstrual periods. Otherwise she was normal. During a pregnancy she had an abundant hemoptysis. Physical examination at that time was negative. An X-ray film of the chest showed an ellipsoid shadow in the left pulmonary field. Search for tubercle bacillus was negative. Tuberculin test was positive. A fungus was recovered from the sputum. Skin tests with trichophytin were positive. The diagnosis of megamycetoma, tumor form, was made. Iodides and later arsenicals were given. Radiographically and clinically the patient improved and up to ten months after the treatment was started she did not have any more hemoptyses.—*Micosis pulmonar a forma tumoral: Megamicetoma, R. Denis, A. P. Heudtlass & J. A. Marti, Bol. d. Hosp. F. Santojanni, 1945, 1: 64.*—(*P. B. Franca*)

Chronic Obliterative Bronchiolitis.—A disseminated fibrosis of the type that one finds in silicosis is occasionally found in chronic purulent obliterative bronchiolitis. This disease is caused by chronic irritation with a corrosive agent. The authors present the case of a 57 year old male who worked in a foundry for twenty-two years, with duties involving sanding of metals. During the last two years there were progressive dyspnea, cyanosis, mucopurulent expectoration, anorexia, loss of weight and hemoptysis. On examination there were mild dyspnea at rest and bilateral sibilant râles. X-ray film was typical of silicosis. Analysis of the dust inhaled showed 10 to 15 per cent silicon dioxide, and iron. On autopsy the main findings were in the lungs, with bronchiectasis, purulent bronchiolitis, and pulmonary sclerosis. There was no evidence of tuberculosis or silicosis.—*Contribution à l'étude radiologique et clinique de la bronchiolite oblitérante purulente chronique accompagnée d'une sclérose prononcée du parenchyme pulmonaire, G. Voluter & F. Sciclounoff, Schweiz. med. Wchnschr., June 2, 1945, 75: 484.*—(*J. Gerstein*)